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# The Influence of the Pituitary Gland on Parturition.

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## I. METABOLISM IMMEDIATELY PRIOR TO AND IMMEDIATELY FOLLOWING PARTURITION.

THE study of "milk fever" in cattle has always presented considerable difficulty, since little is known of the metabolic disturbance, although a good deal of work has been done on blood analyses (Wright and Little,[1] Greig and Dryerre[2]). Much light might be thrown on the many problems associated with "milk fever" and other toxaemias of parturition if a more detailed knowledge of the metabolic reactions towards normal parturition existed.

The researches of Rowe and Eakin,[3] Magee[4] and Pommerenke and others[5] have shown that an increase in the metabolic rate occurs prior to parturition with a sudden drop post-partum. The metabolism is little changed, however, the total heat production of the mother just before parturition being equal to that of mother and young immediately following parturition.

A large amount of work has been done on nitrogen metabolism prior to and immediately following birth. Heinrichsen[6] and Grammatikati[7] found a large increase in the nitrogen output immediately following parturition. The former, and later Longridge,[8] stated this was probably the result of regressive changes in the puerperal female, particularly affecting the uterus. Grammatikati, however, thought that mammary gland changes, especially the formation of milk fat from protein, caused this excessive nitrogen excretion. Mellanby's[9] results showed that whereas an increase in creatin output occurred after parturition, the creatinine remained constant. He also found that the uterine muscle did not contain any creatin. Hoffstrom[10] and Wilson[11] found positive nitrogen balances during the later stages of pregnancy, if an adequate diet were supplied. During the puerperium, however, a negative nitrogen balance occurred which could not be checked by dietary measures (Harding[12]). These changes were accompanied by corresponding changes in the blood non-protein nitrogen (Harding,[13] Plass[14]). A fall occurred in the later months of pregnancy and a sudden rise just before and during

### TABLE I.

*Nitrogen Metabolism (Two-day Periods)*

GOAT I.

| Day | Amount of urine c.c. | Amount of faeces grm. | Amount of milk c.c. | Total Nitrogen Output. | | | | Nitrogen intake grm. | Urinary Nitrogen Partition | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Urine grm. | Faeces grm. | Milk grm. | Total grm. | | Urea grm. | Ammonia grs. | Amino acid grs. | Creatinine grs. | Creatine grs. |
| —8 | 230 | 1046 | — | 13.0010 | 10.4218 | — | 23.4228 | 28.1616 | 11.5234 | 0.2998 | 0.0225 | 0.4987 | 0.1964 |
| —6 | 325 | 1057 | — | 36.8018 | 12.3160 | — | 49.1178 | 28.1616 | 31.9621 | 0.9210 | 0.0886 | 0.8528 | 0.5822 |
| —4 | 400 | 1053 | — | 36.6750 | 15.9200 | — | 52.5950 | 19.8298 | 31.7088 | 1.2005 | 0.1011 | 1.5022 | 0.8631 |
| —2 | 448 | 1076 | — | 26.7348 | 17.8455 | — | 44.5803 | 19.8298 | 22.7838 | 0.8140 | 0.0429 | 1.2656 | 0.8665 |
| 2 | 300 | 1050 | 1860 | 24.6842 | 16.1011 | 11.0266 | 51.8119 | 39.6596 | 20.5984 | 2.3088 | 0.0875 | 0.7360 | 0.6360 |
| 4 | 290 | 1682 | 2020 | 24.0563 | 18.0401 | 16.1721 | 58.2685 | 39.6596 | 20.1340 | 1.2117 | 0.0803 | 0.4860 | 0.3840 |
| 6 | 253 | 1661 | 2000 | 14.2113 | 14.5117 | 15.2395 | 43.9625 | 43.3415 | 12.2248 | 0.8418 | 0.0496 | 0.4416 | 0.1256 |
| 8 | 250 | 1630 | 2250 | 14.5683 | 14.0290 | 15.8896 | 44.4869 | 43.3415 | 12.3286 | 0.6533 | 0.0482 | 0.4088 | 0.1052 |

GOAT II.

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| —10 | 600 | 1110 | — | 18.5017 | 8.0000 | — | 26.5017 | 28.1616 | 15.5679 | 0.3882 | 0.0248 | 0.7109 | 0.5632 |
| —8 | 410 | 1310 | — | 12.0432 | 13.8800 | — | 25.9232 | 28.1616 | 15.6579 | 0.1172 | 0.0186 | 0.5146 | 0.3014 |
| —6 | 1160 | 1370 | — | 37.5794 | 11.9099 | — | 49.4893 | 28.1616 | 32.3777 | 0.6545 | 0.0344 | 1.5405 | 1.4906 |
| —4 | 1160 | 970 | — | 37.7093 | 9.2213 | — | 46.9306 | 28.1616 | 31.5690 | 0.7811 | 0.0483 | 1.4918 | 1.1182 |
| —2 | 870 | 1000 | — | 22.7035 | 6.7263 | — | 29.4298 | 28.1616 | 19.4953 | 0.7649 | 0.1441 | 1.1145 | 0.8178 |
| 2 | 1000 | 1350 | 1760 | 20.4568 | 9.5745 | 11.8991 | 41.9304 | 42.2424 | 17.4062 | 1.0178 | 0.0271 | 1.1570 | 0.8430 |
| 4 | 950 | 1500 | 1760 | 22.9585 | 15.5242 | 13.0126 | 51.4953 | 42.2424 | 20.2958 | 1.0188 | 0.0574 | 0.8550 | 0.4750 |
| 6 | 750 | 1370 | 1800 | 20.8677 | 15.0246 | 12.2167 | 48.1090 | 42.2424 | 17.8983 | 0.8043 | 0.1196 | 0.6533 | 0.5617 |
| 8 | 700 | 1650 | 1700 | 18.0908 | 17.0000 | 11.4569 | 46.5477 | 42.2424 | 15.0910 | 1.0006 | 0.0387 | 0.6671 | 0.5929 |

GOAT III.

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| —10 | 540 | 1210 | — | 21.5610 | 9.1050 | — | 30.6660 | 28.1616 | 18.9872 | 0.4151 | 0.0325 | 0.7615 | 0.6214 |
| —8 | 401 | 1250 | — | 14.2356 | 12.2248 | — | 26.4604 | 28.1616 | 11.1565 | 0.2004 | 0.0276 | 0.6008 | 0.5028 |
| —6 | 1112 | 1280 | — | 40.1052 | 14.3156 | — | 54.4208 | 28.1616 | 34.9515 | 0.7313 | 0.0538 | 1.8286 | 1.4657 |
| —4 | 1150 | 820 | — | 41.0986 | 10.0848 | — | 51.1834 | 28.1616 | 35.2286 | 0.8248 | 0.0922 | 1.7353 | 1.3538 |
| —2 | 865 | 1000 | — | 36.2248 | 10.0010 | — | 46.2258 | 28.1616 | 31.8381 | 0.6765 | 0.1040 | 1.8004 | 1.7212 |
| 2 | 1200 | 1410 | 1780 | 26.3151 | 8.2858 | 10.8582 | 45.4591 | 42.2424 | 22.1763 | 1.0848 | 0.0565 | 1.0506 | 0.9563 |
| 4 | 870 | 1460 | 1820 | 27.0821 | 14.1976 | 14.1765 | 55.4562 | 42.2424 | 23.2484 | 1.0026 | 0.0322 | 1.0022 | 0.8482 |
| 6 | 765 | 1425 | 1960 | 25.2243 | 14.2852 | 14.1828 | 53.6923 | 42.2424 | 21.0973 | 0.8384 | 0.0410 | 0.8372 | 0.6336 |
| 8 | 650 | 1700 | 1960 | 20.0847 | 16.1334 | 13.0873 | 49.3054 | 42.2424 | 17.9982 | 0.9276 | 0.0305 | 0.7118 | 0.5429 |

labour. Harding connected this protein wastage of the early puerperium with the involution of the uterus, as did Murlin[15] and Shaffer.[16] This is, in part at least, untenable in view of Mellanby's researches. Also, creatin still occurs in excess in the urine even after removal of the uterus.

Bar[17] and later Murlin,[18] in a study of the nitrogen partition in the urine during pregnancy, showed that a diminished excretion of urea occurs, with an increase in ammonia output. Bock[19] and Stanojivic[20] found an increase in blood-ammonia during parturition. The latter attributed this to the extreme activity of the smooth and striated muscle. An increase in amino acid nitrogen of the urine has been noted by Wilson.

Although doubt seems to exist regarding the presence of an acidosis during pregnancy, it is a well known fact that prior to, and immediately following labour, an acidosis ensues with a decrease in the alkali reserve (Siedentopf,[21] Solai and others,[22] Peco[23]). Although this decrease occurs all through pregnancy, as term approaches it becomes more marked, culminating immediately following birth. During pregnancy the mother undergoes a great carbohydrate drain, and Schmidt and Wingen[24] believe that this requirement is met in part by fat being converted to carbohydrate in the liver. The lowering of the alkali reserve may therefore be the result of the appearance in the blood-steam of the acid by-products of fat catabolism. On the other hand there is transference of base from the maternal to the foetal tissues. This will require neutralizing reactions on the part of maternal organs and may account for the lowering of the alkali reserve.

With regard to the mineral metabolism a special interest seems to have been attached to an examination of the serum calcium. Early in the puerperium the serum calcium tended to lie at or just below the lower limits of variation (Krebs,[25] Denis,[26] Stander[27]). With mice Bokelmann and Bock[28] found a low calcium concentration of the tissues, showing that a definite decalcification of the mother occurred. Cantarow and others[29] found an increase in diffusible calcium and a marked decrease of non-diffusible, especially in the first stage of labour. Rickert and Palmerlee[30] and Becks[31] showed a decrease of 50 per cent in the calcium content of the saliva during parturition. Vignes[32] attributed many of the pathological symptoms of these periods, as dental caries, tetany, vomiting and eclampsia, to this disturbance of the calcium metabolism. Wright and Little[35] and Greig and Dryerre attributed "milk fever" to this same cause.

Immediately prior to parturition Tarlo and Olerskaya[34] found a decrease in the chloride of sweat and urine and an increase in blood. This they attributed to a change in the water chloride metabolism.

For the experiment on which this paper is based the goat was chosen, since only on very rare occasions is it susceptible to toxaemias during parturition. Its urine and faeces were collected every two days and analysed. After the onset of lactation a sample was taken from each milking and analysed, the result being given for two-day periods. The following results were obtained:

*Output.*

The results (Table I) show an increased output of urine prior to kidding, falling off after the birth of the kid. The faeces increased in amount concurrently with the decreased urinary secretion.

*Nitrogen.*

The results noted in Table I indicate that the urinary nitrogen output was markedly increased prior to parturition, so that the retention was markedly diminished. An increased faecal output also occurred. Post-partum the urinary nitrogen fell rapidly with a more gradual decrease in the faeces. The partition of nitrogen in the urine is of importance in indicating the source of the excess nitrogen.

*Urea.* Prior to parturition there was a definite increase in the amount of urea excreted. As a percentage of the total urinary nitrogen the urea had, however, decreased from about 88 per cent eight days before kidding to 85 per cent two days before, with a further fall to about 83 per cent for four days after parturition.

*Ammonia.* A definite increase occurred in the ammonia output both before and after kidding. The percentage of the total urinary nitrogen excreted by the goat as ammonia, rose only slightly before parturition. Immediately after kidding the percentage suddenly increased, falling off slowly with the onset of lactation. This cannot be explained by a lessened food intake, since the decrease only occurred with one animal to a small extent.

*Amino Acids.* A slight increase occurred both in the total amount and as a percentage of the total urinary nitrogen. The percentage increase was most marked post-partum.

*Creatinine.* An increase in the total output was observed prior to kidding, with a rapid fall post-partum. The percentage increase was small, from about four to five per cent.

## TABLE II.

*Mineral Metabolism (Two-day periods).*

### GOAT I.

| Day | Calcium<br>Urine grm. | Faeces grm. | Milk grm. | Total grm. | Intake grm. | Phosphorus<br>Urine grm. | Faeces grm. | Milk grm. | Total grm. | Intake grm. | Chlorine<br>Urine grm. | Milk grm. | Total grm. | Intake grm. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| —8 | 0.0300 | 2.6760 | — | 2.7060 | 3.7232 | 0.8816 | 15.0882 | — | 15.9698 | 16.3150 | 0.3570 | — | 0.3570 | 0.3128 |
| —6 | 0.0836 | 2.0016 | — | 2.0852 | 3.7232 | 1.2028 | 14.0036 | — | 15.2060 | 16.3150 | 0.7176 | — | 0.7176 | 0.3128 |
| —4 | 0.1044 | 1.9596 | — | 2.0640 | 2.7292 | 1.2016 | 18.7726 | — | 19.9742 | 13.9000 | 1.7610 | — | 1.7610 | 0.2414 |
| —2 | 0.0800 | 2.0816 | — | 2.1616 | 2.7292 | 1.1646 | 18.0000 | — | 19.1646 | 13.9000 | 0.7184 | — | 0.7184 | 0.2414 |
| 2 | 0.0524 | 2.7022 | 2.7400 | 5.4946 | 5.6968 | 0.6010 | 14.2110 | 8.3360 | 23.1480 | 23.4160 | 1.6016 | 3.2110 | 4.8126 | 0.5001 |
| 4 | 0.0400 | 2.4972 | 2.2000 | 4.7372 | 5.6958 | 0.6050 | 14.1198 | 8.0388 | 22.7636 | 23.4160 | 1.4910 | 2.1300 | 3.6210 | 0.5001 |
| 6 | 0.0396 | 2.5130 | 2.4232 | 4.9758 | 6.0884 | 0.8022 | 14.1976 | 8.1794 | 23.1792 | 23.7605 | 1.4364 | 2.2362 | 3.6726 | 0.5001 |
| 8 | 0.0324 | 2.1930 | 2.0864 | 4.3118 | 6.4800 | 0.7708 | 15.2480 | 9.6964 | 25.7152 | 24.1050 | 0.5794 | 2.1026 | 2.6820 | 0.5001 |
| **GOAT II.** | | | | | | | | | | | | | | |
| —10 | 0.0314 | 1.6282 | — | 1.6596 | 3.7232 | 0.3558 | 13.0950 | — | 13.4508 | 16.3150 | 0.3959 | — | 0.3959 | 0.3128 |
| —8 | 0.0926 | 1.1535 | — | 1.2461 | 3.7232 | 0.5149 | 15.0860 | — | 15.6009 | 16.3150 | 0.4601 | — | 0.4601 | 0.3128 |
| —6 | 0.1124 | 1.6556 | — | 1.7680 | 3.7232 | 0.5714 | 18.3440 | — | 18.9154 | 16.3150 | 0.6589 | — | 0.6589 | 0.3128 |
| —4 | 0.1356 | 0.9418 | — | 1.0774 | 3.7232 | 0.7586 | 20.0000 | — | 20.7586 | 16.3150 | 1.5484 | — | 1.5484 | 0.3128 |
| —2 | 0.1040 | 1.1738 | — | 1.2778 | 3.7232 | 0.4009 | 15.1400 | — | 15.5409 | 16.3150 | 0.9142 | — | 0.9142 | 0.3128 |
| 2 | 0.1026 | 1.2040 | 1.9337 | 3.2403 | 5.5938 | 0.3404 | 17.3616 | 6.8874 | 24.5894 | 24.4725 | 1.3774 | 1.3079 | 2.6853 | 0.4692 |
| 4 | 0.0824 | 2.1661 | 2.3317 | 4.5802 | 5.5938 | 0.3800 | 19.0000 | 6.5920 | 25.9720 | 24.4725 | 1.0320 | 1.2170 | 2.2490 | 0.4692 |
| 6 | 0.0656 | 1.6600 | 2.5668 | 4.2924 | 5.5938 | 0.3000 | 13.6700 | 7.0944 | 21.0644 | 24.4725 | 0.7029 | 1.3064 | 2.0093 | 0.4692 |
| 8 | 0.0324 | 2.2581 | 2.5408 | 4.8313 | 5.5938 | 0.2300 | 15.3236 | 6.8520 | 22.4056 | 25.4725 | 0.7405 | 1.1616 | 1.9021 | 0.4692 |
| **GOAT III.** | | | | | | | | | | | | | | |
| —10 | 0.0420 | 1.5984 | — | 1.6404 | 3.7232 | 0.4161 | 14.5106 | — | 14.9267 | 16.3150 | 0.4218 | — | 0.4218 | 0.3128 |
| —8 | 0.0861 | 1.3616 | — | 1.4477 | 3.7232 | 0.4382 | 14.8260 | — | 15.2642 | 16.3150 | 0.3858 | — | 0.3858 | 0.3128 |
| —6 | 0.1004 | 0.8228 | — | 1.9232 | 3.7232 | 0.5020 | 16.1975 | — | 16.6995 | 16.3150 | 0.8562 | — | 0.8562 | 0.3128 |
| —4 | 0.1000 | 1.0406 | — | 1.1406 | 3.7232 | 0.8226 | 18.2248 | — | 19.0474 | 16.3150 | 0.8864 | — | 0.8864 | 0.3128 |
| —2 | 0.1000 | 1.2133 | — | 1.3133 | 3.7232 | 0.6116 | 16.1865 | — | 16.7981 | 16.3150 | 1.9276 | — | 1.9276 | 0.3128 |
| 2 | 0.1158 | 1.0436 | 2.0108 | 3.1702 | 5.5938 | 0.4157 | 18.1123 | 6.5824 | 25.1098 | 24.4725 | 1.4858 | 1.4008 | 2.8866 | 0.4692 |
| 4 | 0.1046 | 2.0018 | 2.3252 | 4.4316 | 5.5938 | 0.4165 | 17.9850 | 7.0176 | 25.4191 | 24.4725 | 1.3362 | 1.4586 | 2.7948 | 0.4692 |
| 6 | 0.0721 | 2.0026 | 2.6956 | 4.7703 | 5.5938 | 0.3500 | 19.1626 | 7.2583 | 26.7709 | 24.4725 | 0.8564 | 1.4017 | 2.2581 | 0.4692 |
| 8 | 0.0564 | 1.9858 | 2.7006 | 4.7428 | 5.5938 | 0.3286 | 13.0982 | 7.0978 | 20.5246 | 24.4725 | 0.7218 | 1.1828 | 1.9046 | 0.4692 |

*Creatin.* A slight but definite increase occurred in both total and percentage output.

*Calcium.*

The results (Table II) show an increased urinary secretion of calcium prior to kidding, with a slow fall post-partum. A slight decrease occurred in the faecal output, the retention remaining, however, practically constant. With the onset of lactation the secretion of milk caused a large decrease in retention.

*Phosphorus.*

In Table II the results show a slight increase in urinary phosphorus before kidding, with a sudden decrease post-partum. Meanwhile an increased faecal output marked the four days preceding and following parturition. This would appear to be due to absorption and re-excretion into the gut since absorption is otherwise normal. A markedly diminished retention was thus seen during this period.

*Chlorine.*

The results (Table II) show an increased urinary output from six days prior to kidding, with a larger increase post-partum. The loss of chlorine in the milk together with the increased urinary output greatly enhanced the negative retention.

## DISCUSSION.

The view has been expressed that the metabolic disturbance occurring at parturition is merely the accumulation of the various factors interfering with normality since the onset of pregnancy. A study of conditions throughout the period of gestation would, therefore, be of value in attempting an interpretation of the foregoing results.

Immediately following conception hypertrophy of the uterine mucosa commences, and it has progressed to a certain degree by the time the fertilized ovum arrives. The outermost cells of this ovum slowly destroy the adjacent cells of the membrane and the ovum sinks in, the membrane growing over the protruding part of the ovum. Concomitantly an enlargement of blood-vessels, especially the venous and capillary systems, occurs. The outermost layer of the epiblast then becomes transformed in order to serve for the embryonic nutrition, which consists in the formation of villi, the chorionic villi. As the foetal blood-vessels form they penetrate into the villi. At this period the foetal villi are immersed in the maternal blood, a double layer of epithelial tissue separating the foetal blood-vessels from the maternal blood.

In the ruminant the placental attachment is intricate and is confined to certain areas covered by the maternal and foetal cotyledons. Thus, with the growth of the young and the consequent tissue deposition by the chorionic villi, it seems probable that there will be discharged into the maternal blood-stream the products of protein autolysis. From the fifth month degeneration of the placenta sets in, and later the ectoderm covering the villi becomes reduced to a single layer of cells which act as an osmotic membrane. Little, however, is known as to the actual mode of transference of food to the foetus. The placenta removes the nitrogenous excreta, thus minimizing the foetal urinary excretion, shown by the low nitrogen content of the amniotic fluid.

That the symptoms of parturition, the drop in temperature, relaxation of the sacro-sciatic ligament and sinking of the pelvic ligament, so similar to those occurring at the end of pseudo-pregnancy of a normal heat period, may be due to reduction in amount of the ovarian hormone or atrophy of the corpus luteum is a possibility brought forward by Hammond.[35] Frequent references have been made to the inessential nature of the corpus luteum during the latter half of pregnancy, Marshall and Jolly[36] claiming that it undergoes involution. This appears doubtful in view of the later work of Corner,[37] Bergmann[38] and Hammond in connexion with size and structure, whereby involution was not apparent.

There is little evidence that either the corpus luteum or uterus prior to parturition is associated with any muscular catabolism. Also Magee, Pommerenke and others have shown conclusively, from work on the basal metabolism of the parturient animal, that muscular catabolism occurring prior to labour is not due merely to stimulation of the body tissues to increased activity.

In view of the work on the heat metabolism of the mother up to and immediately following term, it is of interest to note the weight changes occurring. Gaessner[39] first noted that the increase in weight of the mother was greater than the increase in weight of the foetus and reproductive organs. Hirsch[40] found that the greatest weight occurred six days before the onset of labour, remained steady for two days, and then fell rapidly. Zangemeister[41] corroborated these results in part, but found that the maximum weight of the mother was attained three days prior to labour, followed by a rapid decrease. Hirsch thought this was the result of increased activity of the pituitary, whereas Kemper[42] explained it by the lessened food intake together with an increase in excreting function of the pregnant female. From a consideration of the results in Table I it will be seen that this loss in weight occurs approximately at the time of the increased nitrogen output, with only a slight decrease, if any, in food intake.

From a consideration of the results recorded here it seems possible to formulate a hypothesis as to the chemical pathogenesis of parturition. From four to six days prior to parturition an abnormal protein catabolism occurs, which cannot be the result of an intense acidosis since ketone bodies were not found in the urine. The urinary nitrogen partition products show that this excess nitrogen is of endogenous origin, due to a breakdown of muscular tissue. It seems clear that this muscular catabolism is the result of the presence in the system of some body not present in the normal animal. Turning now to a consideration of the endocrine factors involved in pregnancy and parturition, it is known that, in the earlier and later stages, there is an increase in the activity of the ovary and anterior pituitary lobe, together with increased function of the thyroid, pancreas, adrenals and posterior pituitary. When in the normal animal hypersecretion of one or more of the endocrine organs would lead to an endocrinopathy, in the normal pregnant female a balance is maintained between the increased glandular secretions, without apparently any ill effects. At the end of pregnancy an increased secretion of the posterior lobe of the hypophysis occurs, which, produced under the stimulus of some ovarian substances, would lead to stimulation of the uterus, with consequent parturition (Dixon and Marshall,[43] Heller and Holtz[44]). That posterior lobe injections cause a disturbance of the normal metabolic activities has been amply proven. Hewitt[45] obtained an increased urinary output of ammonia. Buschke[46] and later Poullsson[47] found an increased excretion of chlorine through the urine, while Himwich and Haynes[48] gave results in which little or no change was seen in the basal metabolic rate after injection. Although by no means definite, the facts are very suggestive that the muscular catabolism occurring prior to parturition is caused primarily by the increased content of the posterior lobe hormone in the body tissues. As such, the increased urinary nitrogen of the first four to six days post-partum is probably a combination of the after-effects of the excess of hormone, together with involution of uterine muscle.

## SUMMARY.

1. Six days before the onset of kidding in goats a large increase occurs in the output of nitrogen in the urine. This appears to coincide with the period of maternal loss of weight.

2. The nitrogen partition in the urine shows that a percentage increase occurs in the ammonia, amino acid and creatin fractions.

3. Post-partum the urinary nitrogen falls rapidly back to normal.

4. A large increase in urinary chloride also marks the six days prior to kidding.

5. From general considerations of the changes occurring during pregnancy to the onset of labour, it seems probable that the abnormal metabolic reaction of the mother is the result of increased activity of the posterior lobe of the hypophysis.

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## II. METABOLISM STUDIES DURING INJECTIONS OF EXTRACTS OF THE POSTERIOR LOBE OF THE HYPOPHYSIS.

IN the first paper of this series (Morris[1]) it was shown that the peculiar reaction of the animal body during parturition might be explained by the increased activity of the posterior lobe of the hypophysis. In the present paper a study has been made of the nitrogen metabolism after injections of pituitrin.

The major portion of the experimental work on pituitrin injections has been concerned with the anti-diuretic effect. Some slight variations occur according to the method of administration. Given orally, or subcutaneously, an immediate physiological effect has not been noted, although Hamill[2] found that given by the mouth to cats in full digestion caused certain disturbances of the intestines and uterus. The effect on the urinary secretion also varies according to the mode of injection (Schäfer[3]). An intravenous injection causes a marked diuresis immediately followed by a more prolonged anti-diuresis, and a subcutaneous injection causes anti-diuresis followed by a marked diuresis (Lebermann[4]). Poulsson[5] claims that a true hormone is liberated by the posterior lobe which regulates water excretion by its effect on the proximal renal tubules, increasing water resorption from the glomerular filtrate.

Excessive doses produce strong toxic effects, apparently caused by paralysis of the respiratory centre (Schäfer and Vincent,[6] Garnier and Thaon[7]). In rabbits Conti and Curti[8] noted that the toxic effects may be diminished by the simultaneous administration of thyroid extract and anterior lobe extract.

Little has been done on the effect of pituitrin on the nitrogen metabolism. Schäfer and Vincent and Thaon found a deep-seated metabolic disturbance after long continued injections. Malcolm[9] found a retention of nitrogen while Frey and Kumpiess[10] obtained variable results. Hewitt[11] giving posterior lobe extract with 0.25 gm. thyroid found an increased output of ammonia over that excreted by the thyroid alone. Poulsson, on the other hand, obtained a decrease in ammonia output. Roux and Tallandier[12] noticed an increase in the creatinine output in rabbits injected subcutaneously.

The present series of experiments was conducted on lactating and non-lactating goats. The pituitrin and antuitrin S. (Parke, Davis & Co.) were injected subcutaneously. The experiments are divided into three parts:

1. Increasing doses of pituitrin injected.
2. Three small doses followed rapidly by one large dose.
3. Two doses of antuitrin S. followed by one injection of pituitrin.

In each part there were used two lactating and two non-lactating goats, the urine and faeces being collected every two days.

The results show the total amount of nitrogen and partition products, the percentages being omitted for brevity.

## RESULTS.

*Part I. Lactating Animals.*

Table I shows the results of increasing doses of pituitrin. With only one c.c. injected a fall occurs in the output of urine, faeces and milk, the two latter quickly returned to normal. Increasing the doses causes an increased urinary output but a decreased secretion of milk. An injection of seven c.c. pituitrin also caused a marked increase in faecal output.

With all doses the percentage of nitrogen in the urine is decreased from about 0.32 to 0.24 per cent or less, whereas the total output of urinary nitrogen is increased with the largest dose (seven c.c.) by about 25 per cent. The faecal nitrogen varies very considerably with all doses, but over any period of four to six days after injection is fairly normal. The percentage of nitrogen in the milk is slightly decreased, from about 0.7 to 0.6 per cent.

The urinary partition of nitrogen shows that a slightly increased output of ammonia occurs after injections of three c.c. and seven c.c. of pituitrin, a decrease occurring with the first injection due to the decreased urinary secretion. A decreased percentage of urea, from 83 to 79 per cent is seen whereas the total urea excreted varies with the urinary volume. The amino acid nitrogen shows a tendency to fall after the smaller injections (one c.c. and three c.c.), whereas with the large injection (seven c.c.) an increase is observed even to the eighth day after injection. Little change occurs with the pre-formed creatinine, but an increase in the creatine is very decided.

*Non-lactating animals.*

The general trend of the results is the same as with the lactating goats. The tendency for an increased output of urinary nitrogen, however, is more marked, an increase being noted even after an injection of three c.c. of pituitrin. A more definite increase in ammonia is also noted together with a very large output of urinary creatine, most noted after an injection of seven c.c.

*Part II. Lactating animals.*

Table II shows the effect of three small doses (one c.c.) of pituitrin at intervals followed by one large dose, in one case 18 c.c. and in another 10 c.c. The general trend of the results, especially the secretion of urine, faeces and milk is very similar to those in Part I. In one animal (goat 5) the excretion of urine tends to decrease slightly, whereas in goat 6 a slight increase is noted. In both animals the faecal output is decreased together with a smaller secretion of milk.

The total nitrogen figures show that a markedly increased output occurs in the urine after the large injection (18 c.c. or 10 c.c.) with little change in the faecal and milk nitrogen. The decreased percentage of urea nitrogen output is more marked than in the previous set of experiments (Part I), together with a greatly increased ammonia output. A large increase also occurs in the amino acid nitrogen excreted, whereas there seems to be a tendency for the creatinine and creatine to remain fairly steady or to increase to a small extent.

*Non-lactating animals.*

Once more the same general differences are noted but slightly more marked, the increased urinary nitrogen occurring more quickly after the large injection (10 c.c.) with that of the lactating animals.

*Part III. Lactating animals.*

The effect of a pituitrin injection following two injections of antuitrin S. is seen in Table III. The effect of the antuitrin is to increase urinary excretion, the effect on the nitrogen metabolism being slight, a very small increase in nitrogen excretion resulting. Not any effect on the urinary partition of nitrogen can be noted. An injection of five c.c. of pituitrin, however, gives a slightly increased excretion of urine with a large and fairly rapid increase. The nitrogen partition shows the same changes seen in the two previous series of experiments (Parts I and II) but is more marked and more rapid.

*Non-lactating animals.*

As in two previous series the results for the non-lactating goats are more marked and the increases more rapidly attained than with lactating animals.

## DISCUSSION.

The results in Tables I, II and III show that the action of extracts of the posterior lobe of the hypophysis is of a deep seated origin, corroborating the results of Schäfer and Vincent and Thaon.[13] A detailed examination of the effect of the injections of pituitrin on the urinary nitrogen partition products affords evidence as to the origin of the metabolic disturbance. The three most significant facts are: (*a*) a fall in the percentage of urea nitrogen, (*b*) a rise in the ammonia nitrogen, and (*c*) a rise in the amino-acid nitrogen of the urine. Evidence that normally the liver is the sole agent concerned with urea formation has been clearly given by the work of Bollmann, Mann and Magath[14] who state that "the production of urea in the canine organism is entirely dependent upon the presence of the liver, since urea formation ceases as soon as the liver is extirpated." The locus of production of ammonia, however, is a problem which has never been fully proven. Nash and Benedict[15] in a series of experiments on dogs attempted to prove that only the kidney is associated with ammonia production and that the blood ammonia is merely a leakage. Bliss[16] corroborated the majority of their results but showed, as also did Tashiro and others,[17] that all produce ammonia. An excess of ammonia in the blood is prevented, however, by the formation of urea in the liver. Thus when a decreased percentage of urinary urea is noted, as in the present instance, it is natural to assume partial injury to the liver. This is of interest in view of the results found during parturition in which a similar decrease is noted. The older view that urea was used for tissue formation is apparenty false since a similar reaction is caused by pituitrin. In one respect the results noted here, after injections of the posterior lobe extracts, differ markedly from those of Bollmann and others. They found that after removal of the liver, although there is a shift in the urea and ammonia nitrogen of the urine in favour of the latter, a definite increase in total urinary ammonia does not appear. They conclude that "the liver probably does not have any special part in the production of ammonia." The results of this investigation seem to show that pituitrin, together with its effect on liver function, increases in the animal's body, which cannot be accounted for by increased acidity in the body.

It seems possible to conclude, therefore, that extracts of the posterior lobe of the hypophysis have a deleterious effect on hepatic function. These results are of special interest in view of Fauvet's[18] results. He found that by repeated injections of extracts of the posterior lobe liver injury was obtained, a definite necrosis appearing. With guinea-pigs death resulted after three injections. In the second part of the present series of experiments, goat 1 showed signs of a toxaemia, refusing to eat or drink. It is noticeable, when a comparison is made with goat 6, that the urea nitrogen has fallen very low and the ammonia and amino acid nitrogen have increased far above normal. Also the difference between the total urinary nitrogen and the sum of the urinary partition products has increased from about 2.5 in the normal period to about 10 after the injection of 18 c.c. In all cases a slight increase in this undetermined nitrogen is found. An increased output of hippuric acid has been found after injections of posterior lobe extracts, and it is possible that this is the cause of the difference between the total and the partition nitrogen in the present experiment.

From the results it is apparent that the action of the extract is more rapid with non-lactating animals than with lactating. It would appear that the lactating animal has the ability to overcome the action of toxic agents more readily than the non-lactating. Previous work on a comparison of the effects of certain salts on lactating cows (Mattick and Wright[19]) shows that during lactation the animals can deal more readily with abnormal metabolites. Whether this is due solely to the hormones causing the secretion of milk, or to an increased activity of all glands during lactation is at present unknown.

Heller and Holtz[20] in a series of experiments found that preparations of the anterior hypophysis hormone sensitizes the uterus of infantile and pregnant guinea-pigs to posterior lobe preparations. The results noted in Part III show that the same effect is found on the metabolic reaction of the animal. When the anterior lobe extract was injected prior to the posterior, only a small dose (five c.c.) of the latter was necessary to give the same effect as more than 10 c.c. of pituitrin alone.

In the first paper of this series (Morris) it was shown that during parturition an abnormal metabolism occurred prior to birth. The results in brief showed an increased output of urinary nitrogen, a decreased percentage of urea nitrogen and an increase in ammonia and amino acid nitrogen. It is evident from a comparison that the results obtained immediately prior to parturition and those in the present paper, with special reference to Table III (Part III), are very similar. It is possible, therefore, to conclude that during the last few days of pregnancy an increased flow of the posterior lobe hormone occurs, the primary effect on the animal's body being an abnormal nitrogen metabolism due, apparently to injury of the function of the liver.

## SUMMARY.

1. Small doses of pituitrin cause an anti-diuresis and a decrease in the percentage of urinary nitrogen. Large doses cause first an anti-diuresis followed rapidly by a diuresis. The total urinary nitrogen increases by about 25 per cent.

2. A decrease in the percentage of urea nitrogen is noted with all doses and an increase in ammonia and amino acids.

3. The effect of pituitrin is more rapidly attained in non-lactating animals.

4. Injections of anterior lobe extracts, prior to the pituitrin, sensitize the body to the pituitrin.

5. From a comparison of these results with those obtained during parturition it is concluded that prior to parturition the abnormal metabolism encountered is due to increased flow of the posterior lobe hormone.

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TABLE I.

*Increasing doses of pituitrin.*

GOAT I.

|  |  |  | Total nitrogen |  |  | Urinary parturition of nitrogen |  |  |  |  |  |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Urine c.c. | Faeces grm. | Milk c.c. | Urine grm. | Faeces grm. | Milk grm. | Urea | Ammonia | Amino acid | Creat-inine | Creatine | Remarks |
| 750 | 1300 | 1060 | 22.61 | 14.04 | 7.46 | 18.68 | 1.89 | 0.70 | 0.70 | 0.24 |  |
| 830 | 1200 | 1150 | 21.24 | 12.80 | 7.42 | 17.96 | 1.61 | 0.87 | 0.77 | 0.20 | Normal |
| 620 | 1400 | 720 | 21.91 | 14.60 | 4.45 | 18.72 | 1.97 | 0.72 | 0.69 | 0.30 |  |
| 220 | 1000 | 600 | 5.04 | 7.49 | 3.73 | 3.38 | 0.67 | 0.38 | 0.30 | 0.24 | 1 c.c. injected |
| 500 | 1000 | 1000 | 10.88 | 11.55 | 6.40 | 8.09 | 1.10 | 0.67 | 0.68 | 0.53 |  |
| 640 | 1500 | 1100 | 13.09 | 18.29 | 6.85 | 9.48 | 2.54 | 0.81 | 0.61 | 0.51 |  |
| 720 | 1410 | 1090 | 21.08 | — | — | — | — | — | — | — |  |
| 900 | 1400 | 870 | 17.49 | 11.65 | 5.42 | 12.46 | 2.49 | 0.74 | 0.80 | 0.62 | 3 c.c. injected |
| 1000 | 1300 | 920 | 17.34 | 9.45 | 5.81 | 10.74 | 5.77 | 0.18 | 0.92 | 0.77 |  |
| 1000 | 1400 | 920 | 20.27 | 11.17 | 5.26 | 14.32 | 4.83 | 0.39 | 0.93 | 0.76 |  |
| 760 | 1300 | 880 | 22.51 | 14.57 | 5.42 | 17.47 | 3.25 | 0.91 | 0.74 | 0.53 |  |
| 1140 | 1550 | 890 | 27.99 | 18.89 | 5.87 | 19.75 | 4.65 | 1.40 | 0.66 | 0.92 |  |
| 1050 | 1550 | 865 | 25.89 | 18.95 | 5.79 | 18.68 | 3.95 | 1.04 | 0.67 | 0.89 | Normal |
| 1090 | 1800 | 890 | 27.03 | 20.22 | 6.16 | 20.00 | 3.68 | 1.68 | 0.69 | 0.86 |  |
| 1280 | 2100 | 930 | 28.99 | 25.63 | 6.20 | 21.18 | 4.51 | 2.10 | 0.74 | 1.33 | 7 c.c. injected |
| 1100 | 2050 | 965 | 28.65 | 13.36 | 6.62 | 20.80 | 4.00 | 1.65 | 0.81 | 1.12 |  |
| 1180 | 2100 | 1045 | 32.23 | 20.12 | 5.55 | 22.06 | 3.56 | 3.92 | 0.63 | 1.13 |  |
| 1160 | 2000 | 1050 | 30.04 | 13.03 | 5.40 | 20.56 | 4.63 | 3.23 | 0.64 | 0.99 |  |

TABLE I (*continued*).

GOAT 2.

| Urine c.c. | Faeces grm. | Milk c.c. | Total nitrogen Urine grm. | Faeces grm. | Milk grm. | Urinary parturition of nitrogen Urea | Ammonia | Amino acid | Creat-inine | Creatine | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1960 | 2730 | 2900 | 27.96 | 23.21 | 14.01 | 19.89 | 4.25 | 1.36 | 0.76 | 0.42 | |
| 2020 | 2425 | 2930 | 29.24 | 20.15 | 14.18 | 20.76 | 4.09 | 1.48 | 0.79 | 0.56 | Normal |
| 2000 | 2680 | 2910 | 29.00 | 26.23 | 14.02 | 20.00 | 4.29 | 1.44 | 0.75 | 0.47 | |
| 850 | 1720 | 1780 | 10.98 | 14.26 | 5.22 | 7.27 | 2.15 | 0.76 | 0.57 | 0.38 | 1 c.c. injected |
| 1430 | 2200 | 1790 | 16.21 | 18.32 | 5.35 | 10.14 | 3.43 | 1.04 | 0.62 | 0.49 | |
| 1620 | 1890 | 2500 | 24.44 | 15.95 | 9.68 | 16.05 | 4.28 | 1.28 | 0.84 | 0.65 | |
| 2040 | 2700 | 3000 | 30.28 | 27.09 | 14.56 | 21.23 | 4.38 | 1.49 | 0.79 | 0.49 | |
| 2800 | 2625 | 2320 | 21.56 | 17.86 | 12.96 | 11.18 | 5.15 | 1.85 | 0.86 | 0.57 | 3 c.c. injected |
| 3000 | 2425 | 2525 | 24.78 | 24.12 | 13.54 | 14.96 | 6.28 | 2.04 | 0.91 | 0.59 | |
| 3150 | 2832 | 2415 | 29.05 | 23.56 | 13.75 | 19.89 | 6.04 | 2.00 | 0.93 | 0.68 | |
| 2210 | 2765 | 2728 | 29.28 | 26.26 | 14.11 | 20.16 | 4.98 | 1.57 | 0.80 | 0.60 | |
| 3500 | 3025 | 3010 | 31.47 | 24.18 | 14.36 | 19.06 | 5.25 | 3.15 | 0.81 | 1.21 | 7 c.c. injected |
| 4100 | 3510 | 2725 | 35.28 | 25.05 | 13.28 | 21.24 | 6.15 | 2.98 | 0.89 | 1.35 | |
| 3410 | 3020 | 2975 | 34.33 | 22.91 | 14.11 | 21.58 | 6.72 | 3.43 | 0.93 | 0.99 | |
| 3635 | 2431 | 2896 | 36.05 | 23.36 | 13.87 | 22.96 | 5.40 | 2.15 | 0.78 | 1.12 | |
| 2620 | 2922 | 2910 | 30.18 | 26.23 | 13.99 | 21.05 | 4.70 | 1.88 | 0.81 | 0.84 | |

TABLE I (*continued*).

GOAT 3.

| Urine | Faeces | Total nitrogen |  | Urinary parturition of nitrogen |  |  |  |  |  |
|---|---|---|---|---|---|---|---|---|---|
| c.c. | grm. | Urine grm. | Faeces grm. | Urea | Ammonia | Amino acid | Creat-inine | Creatine | Remarks |
| 850 | 1250 | 28.10 | 22.86 | 20.05 | 4.00 | 0.98 | 0.81 | 0.40 |  |
| 920 | 1300 | 27.65 | 24.22 | 19.74 | 3.26 | 1.01 | 0.74 | 0.43 | Normal |
| 880 | 1120 | 28.77 | 23.15 | 20.23 | 4.16 | 1.44 | 0.77 | 0.36 |  |
| 350 | 860 | 12.38 | 15.22 | 7.85 | 2.00 | 0.62 | 0.48 | 0.24 | 1 c.c. injected |
| 670 | 1020 | 19.25 | 21.35 | 13.11 | 3.61 | 1.00 | 1.15 | 0.57 |  |
| 800 | 1185 | 27.98 | 22.98 | 19.91 | 4.09 | 1.35 | 0.78 | 0.41 |  |
| 950 | 1182 | 25.28 | 20.14 | 14.09 | 4.78 | 1.72 | 1.10 | 0.72 | 3 c.c. injected |
| 1035 | 1226 | 33.14 | 19.29 | 19.87 | 6.24 | 1.85 | 1.35 | 0.85 |  |
| 965 | 1257 | 32.09 | 23.15 | 21.25 | 5.76 | 2.23 | 0.76 | 0.70 |  |
| 872 | 1175 | 28.76 | 25.02 | 20.32 | 4.36 | 1.28 | 0.82 | 0.64 |  |
| 1320 | 1420 | 37.28 | 27.28 | 24.76 | 7.32 | 1.53 | 0.98 | 1.98 | 7 c.c. injected |
| 2010 | 1648 | 48.15 | 29.15 | 32.25 | 8.44 | 2.76 | 1.25 | 1.79 |  |
| 1855 | 1235 | 42.22 | 24.36 | 28.36 | 7.10 | 2.48 | 1.46 | 1.46 |  |
| 1410 | 1710 | 37.26 | 30.22 | 24.13 | 6.03 | 1.95 | 1.29 | 1.85 |  |
| 985 | 1400 | 29.13 | 26.87 | 21.09 | 4.28 | 1.32 | 0.85 | 1.07 |  |

TABLE I *(continued)*.

GOAT 4.

| | | Total nitrogen | | | Urinary parturition of nitrogen | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Urine | Faeces | Urine | Faeces | | | Amino | Creat- | | |
| | Amino | Creat- | | | Ammonia | Acid | inine | Creatine | Remarks |
| 760 | 1425 | 23.51 | 24.28 | 16.14 | 3.24 | 0.75 | 0.76 | 0.24 | |
| 730 | 1478 | 23.02 | 25.16 | 15.98 | 3.05 | 0.92 | 0.78 | 0.26 | |
| 695 | 1502 | 22.76 | 24.93 | 15.54 | 3.12 | 0.83 | 0.77 | 0.32 | |
| 150 | 702 | 5.12 | 14.23 | 3.15 | 0.68 | 0.21 | 0.21 | 0.09 | 1 c.c. injected |
| 260 | 1235 | 7.55 | 19.16 | 4.59 | 1.05 | 0.46 | 0.48 | 0.24 | |
| 740 | 1400 | 21.98 | 23.22 | 14.04 | 3.20 | 0.85 | 0.76 | 0.27 | |
| 760 | 922 | 18.85 | 21.98 | 10.27 | 2.56 | 0.93 | 1.24 | 0.43 | 3 c.c. injected |
| 850 | 1020 | 29.24 | 25.66 | 17.85 | 4.47 | 1.58 | 1.76 | 0.35 | |
| 830 | 1635 | 31.22 | 24.73 | 20.22 | 5.01 | 2.02 | 0.98 | 0.46 | |
| 725 | 1420 | 23.05 | 24.99 | 16.04 | 3.34 | 1.06 | 0.79 | 0.35 | |
| 1025 | 1235 | 27.36 | 23.16 | 14.28 | 5.16 | 1.93 | 1.45 | 1.04 | 7 c.c. injected |
| 1042 | 1895 | 39.12 | 27.25 | 22.23 | 8.29 | 2.84 | 1.56 | 0.79 | |
| 2156 | 1302 | 38.22 | 22.98 | 24.17 | 8.35 | 3.21 | 1.35 | 0.86 | |
| 1203 | 2005 | 32.15 | 32.24 | 24.36 | 6.15 | 2.15 | 0.99 | 1.43 | |
| 825 | 1590 | 24.28 | 25.63 | 16.92 | 4.73 | 1.24 | 0.78 | 0.62 | |

TABLE II.

GOAT 5.

| Urine c.c. | Faeces grm. | Milk c.c. | Total nitrogen Urine grm. | Faeces grm. | Milk grm. | Urinary parturition of nitrogen Urea | Ammonia | Amino acid | Creat-inine | Creatine | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2005 | 2620 | 2745 | 28.98 | 23.11 | 13.98 | 20.01 | 4.22 | 1.42 | 0.75 | 0.49 | Normal |
| 2050 | 2300 | 2750 | 29.45 | 20.12 | 14.09 | 20.79 | 4.45 | 1.54 | 0.76 | 0.51 | |
| 2000 | 2750 | 2720 | 28.20 | 25.88 | 13.60 | 19.00 | 4.63 | 1.30 | 0.73 | 0.40 | |
| 1720 | 2450 | 2130 | 25.15 | 21.05 | 10.56 | 12.45 | 7.06 | 2.60 | 0.51 | 0.85 | 1 c.c. injected |
| 1500 | 2600 | 2110 | 38.03 | 24.36 | 10.50 | 21.04 | 7.95 | 5.20 | 0.62 | 0.75 | 1 c.c. injected |
| 1350 | 2300 | 1810 | 32.87 | 14.70 | 8.55 | 14.45 | 6.44 | 5.07 | 0.54 | 0.75 | 1 c c. injected |
| 1910 | 2200 | 1770 | 37.04 | 18.32 | 7.89 | 18.44 | 7.57 | 6.15 | 0.46 | 0.25 | 18 c.c. injected |
| 1750 | 2000 | 1880 | 38.73 | 12.30 | 8.55 | 17.25 | 10.92 | 4.45 | 0.70 | 0.58 | |
| 1770 | 2300 | 1850 | 40.35 | 20.67 | 8.86 | 19.66 | 9.09 | 4.83 | 0.76 | 0.34 | |
| 1800 | 2000 | 1900 | 59.91 | 17.84 | 8.92 | 24.86 | 16.14 | 7.48 | 0.39 | 0.82 | |
| 1400 | 1750 | 1800 | 45.21 | 15.28 | 8.34 | 18.95 | 9.22 | 8.21 | 0.41 | 0.48 | Animal not eating<br>Experiment stopped. |

TABLE II (*continued*).

GOAT 6.

| Urine c.c. | Faeces grm. | Milk c.c. | Total nitrogen<br>Urine grm. | Faeces grm. | Milk grm. | Urinary parturition of nitrogen<br>Urea | Ammonia | Amino acid | Creat-inine | Creatine | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1230 | 1485 | 985 | 27.95 | 20.29 | 5.14 | 20.28 | 3.18 | 0.97 | 0.82 | 0.22 | Normal |
| 1085 | 1522 | 1020 | 26.28 | 21.36 | 5.87 | 19.76 | 3.22 | 1.04 | 0.85 | 0.26 | |
| 1222 | 1506 | 1000 | 28.04 | 21.08 | 5.76 | 20.77 | 3.47 | 1.11 | 0.80 | 0.20 | |
| 625 | 1060 | 720 | 14.28 | 16.35 | 3.62 | 8.58 | 4.01 | 1.22 | 0.46 | 0.34 | 1 c.c. injected |
| 540 | 975 | 800 | 17.56 | 15.21 | 4.15 | 10.14 | 5.24 | 1.57 | 0.57 | 0.46 | 1 c.c. injected |
| 670 | 1085 | 850 | 23.22 | 17.11 | 4.54 | 12.26 | 7.81 | 2.83 | 0.78 | 0.28 | 1 c.c. injected |
| 1035 | 1236 | 1000 | 29.24 | 20.27 | 5.84 | 15.93 | 8.21 | 3.46 | 0.65 | 0.75 | 10 c.c. injected |
| 1450 | 1730 | 875 | 36.10 | 24.19 | 4.59 | 18.04 | 12.15 | 3.05 | 1.04 | 1.00 | |
| 1680 | 1220 | 820 | 42.51 | 21.38 | 4.73 | 21.22 | 10.22 | 6.18 | 0.82 | 0.86 | |
| 1475 | 1540 | 1040 | 46.30 | 25.04 | 5.80 | 22.48 | 17.01 | 4.27 | 1.11 | 1.46 | |
| 1285 | 1600 | 1000 | 31.95 | 24.96 | 5.77 | 16.99 | 8.27 | 3.15 | 1.00 | 0.62 | |
| 1200 | 1560 | 995 | 26.28 | 23.22 | 5.38 | 19.28 | 4.04 | 2.26 | 0.90 | 0.35 | |

TABLE II (*continued*).

GOAT 7.

| Urine c.c. | Faeces grm. | Total nitrogen Urine grm. | Total nitrogen Faeces grm. | Urinary parturition of nitrogen Urea | Ammonia | Amino acid | Creat-inine | Creatine | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 1460 | 2430 | 29.27 | 37.28 | 21.25 | 2.98 | 0.99 | 0.80 | 0.26 | |
| 1520 | 2516 | 30.13 | 40.12 | 22.76 | 3.14 | 1.01 | 0.81 | 0.38 | Normal |
| 1485 | 2242 | 29.58 | 36.39 | 22.20 | 2.86 | 0.98 | 0.76 | 0.31 | |
| 840 | 1710 | 17.85 | 24.24 | 9.57 | 3.85 | 2.44 | 1.05 | 0.47 | 1 c.c. injected |
| 720 | 1825 | 25.22 | 26.15 | 14.11 | 5.21 | 4.15 | 1.48 | 0.56 | 1 c.c. injected |
| 610 | 1415 | 33.14 | 22.22 | 15.09 | 8.94 | 6.77 | 1.27 | 0.42 | 1 c.c. injected |
| 1100 | 1295 | 45.98 | 20.47 | 21.35 | 12.31 | 8.95 | 2.44 | 0.98 | 10 c.c. injected |
| 1730 | 1560 | 54.24 | 25.37 | 24.27 | 16.48 | 12.24 | 3.15 | 0.77 | |
| 2040 | 2730 | 43.19 | 42.18 | 22.56 | 12.24 | 6.27 | 2.04 | 1.04 | |
| 2200 | 1482 | 35.28 | 22.95 | 18.98 | 10.47 | 3.58 | 1.36 | 0.62 | |
| 1560 | 2630 | 32.11 | 38.17 | 19.24 | 5.36 | 4.15 | 1.39 | 0.35 | |
| 1500 | 2425 | 30.09 | 36.28 | 21.97 | 4.96 | 2.73 | 0.92 | 0.41 | |

TABLE II (*continued*).

GOAT 8.

| Urine c.c. | Faeces grm. | Total nitrogen Urine grm. | Faeces grm. | Urinary parturition of nitrogen Urea | Ammonia | Amino acid | Creat-inine | Creatine | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 1820 | 2402 | 30.14 | 31.44 | 22.27 | 3.14 | 1.00 | 0.72 | 0.21 | |
| 1860 | 2715 | 31.02 | 29.86 | 22.93 | 3.46 | 1.15 | 0.68 | 0.35 | Normal |
| 1815 | 2516 | 27.28 | 33.57 | 20.04 | 2.75 | 1.26 | 0.76 | 0.28 | |
| 1230 | 1210 | 18.20 | 20.29 | 9.36 | 5.11 | 2.64 | 0.48 | 0.58 | 1 c.c. injected |
| 1460 | 1420 | 20.35 | 22.76 | 10.04 | 5.27 | 3.72 | 0.56 | 0.75 | 1 c.c. injected |
| 845 | 1685 | 24.27 | 24.24 | 11.35 | 18.39 | 3.26 | 0.49 | 0.84 | 1 c.c. injected |
| 762 | 1240 | 32.09 | 20.77 | 16.09 | 10.18 | 4.44 | 1.01 | 0.42 | 10 c.c. injected |
| 1430 | 2500 | 31.22 | 32.19 | 14.22 | 10.93 | 5.73 | 0.89 | 0.57 | |
| 2054 | 1236 | 48.96 | 20.04 | 24.95 | 15.99 | 6.01 | 0.76 | 0.65 | |
| 2546 | 1985 | 47.28 | 25.98 | 25.16 | 16.22 | 3.28 | 0.98 | 1.02 | |
| 3000 | 2720 | 49.10 | 32.86 | 25.98 | 16.87 | 4.19 | 0.62 | 1.14 | |
| 1855 | 3255 | 38.26 | 37.04 | 23.65 | 10.76 | 2.48 | 0.75 | 0.77 | |
| 1920 | 2809 | 33.00 | 33.28 | 23.19 | 5.19 | 2.05 | 0.69 | 0.58 | |

### TABLE III

*Sensitizing effect of the anterior lobe on the posterior.*

GOAT 9.

| Urine c.c. | Faeces grm. | Milk c.c. | Total nitrogen Urine grm. | Total nitrogen Faeces grm. | Total nitrogen Milk grm. | Urinary parturition of nitrogen Urea | Urinary parturition of nitrogen Ammonia | Urinary parturition of nitrogen Amino acid | Urinary parturition of nitrogen Creat-inine | Urinary parturition of nitrogen Creatine | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 800 | 1200 | 740 | 18.84 | 13.50 | 5.46 | 13.31 | 1.44 | 0.52 | 0.68 | 1.07 | Normal |
| 640 | 1250 | 780 | 14.30 | 16.40 | 5.51 | 9.19 | 0.87 | 0.49 | 0.76 | 0.93 | |
| 580 | 1700 | 750 | 17.14 | 15.86 | 5.34 | 12.64 | 1.06 | 0.50 | 0.71 | 1.03 | |
| 1125 | 2000 | 730 | 21.03 | 20.74 | 5.51 | 15.25 | 1.15 | 0.62 | 0.80 | 1.00 | 3 c.c. antuitrin S. |
| 1370 | 1200 | 690 | 22.28 | 14.10 | 5.48 | 15.98 | 1.29 | 0.47 | 0.69 | 1.14 | |
| 950 | 1255 | 659 | 20.76 | 14.09 | 5.02 | 14.36 | 2.04 | 0.53 | 0.72 | 1.48 | 3 c.c. antuitrin S. |
| 780 | 1400 | 592 | 17.68 | 16.23 | 5.19 | 10.04 | 4.32 | 1.35 | 0.94 | 2.56 | 5 c.c. pituitrin |
| 1260 | 1062 | 610 | 27.45 | 9.14 | 5.22 | 14.21 | 6.98 | 3.27 | 0.87 | 1.97 | |
| 1500 | 1670 | 670 | 35.22 | 14.35 | 5.76 | 20.02 | 9.83 | 3.51 | 1.05 | 2.35 | |
| 1095 | 1700 | 580 | 24.35 | 20.28 | 4.97 | 14.78 | 6.25 | 1.97 | 0.76 | 1.22 | |
| 802 | 1430 | 760 | 19.16 | 16.85 | 6.24 | 14.21 | 3.00 | 0.83 | 0.75 | 1.05 | |

TABLE III (*continued*).

GOAT 10.

| | | | Total nitrogen | | | Urinary parturition of nitrogen | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Urine c.c. | Faeces grm. | Milk c.c. | Urine grm. | Faeces grm. | Milk grm. | Urea | Ammonia | Amino acid | Creat-inine | Creatine | Remarks |
| 2230 | 1560 | 1535 | 20.25 | 12.62 | 10.98 | 14.86 | 2.09 | 1.43 | 0.82 | 0.46 | |
| 2050 | 1480 | 1542 | 19.76 | 11.89 | 10.97 | 14.15 | 2.78 | 1.85 | 0.78 | 0.59 | Normal |
| 2175 | 1720 | 1520 | 21.48 | 10.76 | 10.76 | 15.22 | 2.97 | 2.02 | 0.78 | 0.38 | |
| 3500 | 1850 | 1410 | 28.51 | 11.14 | 9.85 | 20.75 | 3.51 | 2.44 | 0.81 | 0.49 | 3 c.c. antuitrin S. |
| 3015 | 1460 | 1455 | 25.22 | 9.21 | 10.02 | 18.24 | 3.48 | 1.95 | 0.75 | 0.57 | |
| 3725 | 1750 | 1200 | 30.04 | 10.97 | 8.44 | 22.83 | 2.99 | 2.07 | 0.84 | 0.58 | 3 c.c. antuitrin S. |
| 1860 | 1245 | 1570 | 20.29 | 7.74 | 11.29 | 10.45 | 5.24 | 3.36 | 0.96 | 0.62 | 5 c.c. pituitrin |
| 2535 | 2010 | 1685 | 36.58 | 10.84 | 12.02 | 18.98 | 9.17 | 5.18 | 1.51 | 1.47 | |
| 2740 | 1475 | 1572 | 44.27 | 9.27 | 11.81 | 27.79 | 10.55 | 5.24 | 1.48 | 1.98 | |
| 1965 | 1765 | 1410 | 37.38 | 10.02 | 10.28 | 22.51 | 4.32 | 7.87 | 0.75 | 1.27 | |
| 2282 | 1590 | 1530 | 24.27 | 11.47 | 11.02 | 18.26 | 2.51 | 2.09 | 0.84 | 1.09 | |

TABLE III (*continued*).

GOAT II.

| | | Total nitrogen | | Urinary parturition of nitrogen | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Urine c.c. | Faeces grm. | Urine grm. | Faeces grm. | Urea | Ammonia | Amino acid | Creatinine | Creatine | Remarks |
| 1840 | 1765 | 26.15 | 14.98 | 18.85 | 1.24 | 0.51 | 0.86 | 0.23 | |
| 1790 | 1875 | 24.26 | 15.75 | 17.02 | 1.09 | 0.47 | 0.79 | 0.43 | Normal |
| 1860 | 1790 | 25.87 | 15.22 | 18.15 | 1.32 | 0.62 | 0.77 | 0.37 | |
| 2240 | 1785 | 30.14 | 15.51 | 22.67 | 1.51 | 0.75 | 0.84 | 0.44 | 3 c.c. antuitrin S. |
| 2500 | 1822 | 34.09 | 15.83 | 26.85 | 1.75 | 0.48 | 0.72 | 0.56 | |
| 2755 | 1710 | 36.25 | 14.23 | 28.99 | 1.22 | 0.51 | 0.86 | 0.27 | 3 c.c. antuitrin S. |
| 1422 | 1850 | 21.02 | 15.14 | 11.02 | 4.34 | 3.34 | 1.14 | 1.55 | 5 c.c. pituitrin |
| 2315 | 1702 | 44.85 | 14.92 | 24.34 | 8.98 | 7.56 | 0.99 | 2.48 | |
| 2918 | 1225 | 59.48 | 10.36 | 30.98 | 15.11 | 12.28 | 1.76 | 2.57 | |
| 2400 | 1935 | 48.20 | 16.27 | 27.43 | 6.83 | 8.19 | 1.65 | 3.12 | |
| 1955 | 1470 | 31.35 | 12.39 | 20.11 | 7.11 | 1.97 | 0.86 | 1.77 | |
| 1840 | 1860 | 27.29 | 16.01 | 20.02 | 2.42 | 0.99 | 0.86 | 0.87 | |

TABLE III *(continued)*.

GOAT 12.

| Urine c.c. | Faeces grm. | Total nitrogen Urine grm. | Total nitrogen Faeces grm. | Urinary parturition of nitrogen Urea | Urinary parturition of nitrogen Ammonia | Urinary parturition of nitrogen Amino acid | Urinary parturition of nitrogen Creatinine | Urinary parturition of nitrogen Creatine | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 840 | 1000 | 27.96 | 16.34 | 22.86 | 2.59 | 0.24 | 0.82 | 1.02 | Normal |
| 1130 | 1250 | 31.69 | 17.76 | 26.29 | 3.54 | 0.29 | 0.77 | 1.48 | |
| 1020 | 1100 | 30.04 | 15.90 | 25.12 | 3.13 | 0.21 | 0.80 | 1.28 | |
| 900 | 1200 | 32.09 | 17.29 | 26.97 | 3.96 | 0.32 | 0.83 | 1.40 | 3 c.c. antuitrin S. |
| 2005 | 1550 | 44.97 | 22.21 | 38.98 | 4.02 | 0.51 | 0.76 | 1.55 | 3 c.c. antuitrin S. |
| 1830 | 1450 | 42.22 | 20.21 | 37.04 | 4.11 | 0.39 | 0.76 | 1.00 | 5 c.c. pituitrin |
| 1430 | 1130 | 56.22 | 14.08 | 36.75 | 8.72 | 3.43 | 1.24 | 2.47 | |
| 2510 | 1540 | 68.48 | 22.46 | 40.84 | 15.04 | 7.29 | 0.85 | 3.51 | |
| 2022 | 956 | 59.77 | 15.15 | 37.29 | 14.27 | 4.22 | 0.76 | 2.22 | |
| 1540 | 1310 | 43.12 | 17.98 | 28.36 | 9.17 | 3.19 | 1.11 | 1.76 | |
| 1095 | 1155 | 32.24 | 16.23 | 25.11 | 5.26 | 0.48 | 0.82 | 1.80 | |

## III. THE POSTERIOR LOBE OF THE HYPOPHYSIS AND THE WATER BALANCE.

THE anti-diuretic action of the posterior lobe hormone on anaesthetized animals has long been known, but the mode of action is still unknown. In 1926 Schäfer[1] wrote, "As regards the anti-diuretic autacoid, it is possible that this does not necessarily act directly on the kidney but may influence it by regulating the amount of water absorbed by the tissues." Tangl and Hazay[2] by perfusion experiments on the excised frog's kidney and in the living animal claim that the pituitary hormone has both an extra-renal and a direct renal action, probably on the convoluted tubules. Kurose[3] thought that anti-diuresis was caused by contraction of the renal blood-vessels, whereas Ross and Stehle[4] found a diminution of urinary secretion even without a fall of blood-pressure. Poulsson[5] also concluded that no change in circulation could account for the anti-diuresis and that no change occurred with glomerular filtration. He stated that diminution was due to increased water resorption in the proximal tubules. A typical shift of water between blood and tissues could not be found, and Poulsson postulated a true hormone of the posterior lobe regulating water metabolism by its effect on the proximal renal tubules. During pituitrin anti-diuresis McIntyre and Van Dyke[6] found an increase in the water content of both cells and serum. This was confirmed by Heller and Smirk[7] who also showed an increased water storage in muscle and serous cavities, thus corroborating the previous work of Pick.[8] That this was not due to any physico-chemical change in the tissue protein was shown by Heller.[9]

The earlier researches of Molitor and Pick[10] on the effect of urea and glucose on the anti-diuresis seemed to show that the sole effect of the posterior lobe extract was on the tissues.

In two previous papers (Morris and Morris[11, 12]) it has been shown that there exists in blood and tissues an organic chlorine compound. The importance of this molecule in the blood and tissues can be recognized from the fact that the chlorine, being organically combined, can take no part in the regulation of the acid-base equilibrium of the body. Various compounds can, however, increase or decrease the amount of chlorine organically combined. When a decrease occurs the chlorine is split off and is then present in the body fluids as ionic chlorine, capable of affecting the osmotic pressure. The present series of experiments was undertaken to discover if any connexion existed between this organic chlorine and the anti-diuresis caused by posterior lobe extract.

## EXPERIMENTAL.

The following series of experiments was performed on two lactating and two non-lactating goats. All four animals were about four years old and weighed about 35 kilogrammes. Table I shows the effect of increasing doses of pituitrin on the excretion of urine, total blood chlorides and organic chlorides. Table II gives the results of three small doses in succession. The urine was collected every two days, the normal being the average for three collections. The pituitrin was injected subcutaneously. The method for calculating column 6, "water retained," is: the ionic chlorine is converted to milligrams of chlorine per 100 c.c. of blood, and the blood volume of the goat is taken as eight per cent of the live weight. Taking goat 1 for the first two periods, normal and one c.c. pituitrin. Converting the ionic chlorine the figures are 291 and 313 milligrams per 100 c.c. Since in normal blood the ionic chlorine is present at a concentration of 291 milligrams per 100 c.c., to maintain the osmotic pressure of the blood intact the 313 milligrams of chlorine will require an addition to the blood of

$$\frac{313}{291} \times 100 - 100 \text{ c.c. water per } 100 \text{ c.c.}$$

For a total blood volume of 2.8 litres this will mean

$$\left(\frac{313}{291} \times 100 - 100\right) \times 28 \text{ c.c. water, i.e. } 301 \text{ c.c.}$$

## EFFECT OF SMALL DOSES.

It will be found that the calculated figures for water retained when pituitrin was injected are always less than the amount actually found. It must be remembered that the calculations are made using blood only, whereas there is organic chlorine in the tissues also (Morris, Watson and Morris[13]). It would be almost impossible to assess the actual value of their contribution to the water metabolism since the weights of the various tissues are not accurately known. Also variations in the organic chlorine may vary, especially in the muscles, which is about 16 to 17 per cent of the live weight of ruminants. It seems, therefore, that when pituitrin is injected in small doses (1 c.c. per 35-40 kilograms) the anti-diuretic action is caused by a conversion of the organic chlorine of the blood and tissues to ionic chlorine. The result is the increased osmotic pressure of both blood and tissues with a consequent retention of water to maintain osmotic equilibrium.

A rough approximation of the total organic chlorine of the body may be obtained for the goat by using the tissue weights found for a goat of average weight, 35.40 kilograms. The figures (Table III) for the total and organic chlorine were obtained from one animal. Were all the organic chlorine transformed into ionic chlorine the retention of water to maintain osmotic equilibrium can now be calculated (Table IV). For the goat, approximately 3,500 c.c. of water should be retained by the body tissues, excluding the blood, by conversion of organic to ionic chlorine. This, however, would only hold when no interference with renal function was found. When the compound, which had the ability to transform the chlorine in the body, had, at the same time, a diuretic action, i.e. the ability to increase the urinary output, the retention of water by the body, blood and tissues, would depend on the strength of the diuresis.

## Effect of Large Doses.

Increasing the dose of pituitrin (Table V) gives an altogether different effect on the water metabolism. Although the organic chlorine has disappeared there is a diuresis, the urinary output after injection being greater than before, for the two-day period of measurement. Attention must be drawn to the fact that the major portion of the urine was excreted on the second day of each of the first two-day periods after injection. It would appear from these results that the pituitrin acts on the renal tissue, causing diuresis, together with the action on the organic chlorine of the body which causes an anti-diuresis. From the fact that during the first day after injection the urinary output is small it is clear that the first action of the pituitrin, when injected subcutaneously, is on the organic chlorine causing retention of water. The more important reaction is on the renal cells, the diuresis, with the elimination of the water retained and some of the water normally held in the fluids and tissues of the body.

It now seems possible to explain the apparently contradictory results obtained by intravenous and subcutaneous injections of posterior lobe extracts. With an intravenous injection of small doses of pituitary extract a temporary diminution of urinary output is followed by a marked diuresis. This, in turn, is followed by a diminution. With subcutaneous injections, on the other hand, a great diminution occurs in urinary excretion. In guinea-pigs and rabbits Houssay and others[14, 15] found a decrease in urinary output after subcutaneous injection; after intravenous injection a marked diuresis occurred. Intravenously the extract is rapidly carried to the kidneys where it has a direct action on the renal cells causing almost immediately a diuresis. When injected subcutaneously filtration into the blood is slow enough to allow the extract to transform the organic chlorine to ionic chlorine and so allow the anti-diuresis to appear. These facts are in complete agreement with the findings of Steggerda.[15] He has shown that pituitrin has no effect on the water absorbing capacity of the frog's isolated gastrocnemius muscle. In live animals, however, pituitrin caused an increase in weight of 14 to 15 per cent, the gastrocnemius muscle showing a corresponding increase. The results in the present paper are also in harmony with those of Fromherz[17] who found that the injection of pituitrin in dogs one hour before giving excess water did not check the diuresis, but tended to accelerate it.

## SUMMARY.

1. It has been shown that posterior lobe extracts affect the blood chlorides, transforming the organic chlorine to the ionic state.

2. The diminution in organic chlorine, by increasing the osmotic pressure of the blood, will cause retention of water. It seems probable that the anti-diuretic action is not renal but is caused by this change in the nature of the blood chlorides.

3. Large injections of pituitrin cause diuresis, which seems to be the sole action of the extract on the renal cells.

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TABLE I.

*Increasing doses of pituitrin.*

| Period | c.c. urine | Total blood chlorine m.Eq. | Organic chlorine m.Eq. | Ionic chlorine of blood m.Eq. | c.c. water retained by calculation | Decrease in urine |
|---|---|---|---|---|---|---|
| | | Goat 1. | Lactating. | 35 kg. | | |
| Normal | 733 | 92.8 | 10.9 | 81.9 | — | — |
| 1 c.c. pit. (day 1–2) | 220 | 93.1 | 4.9 | 88.2 | 224 | 513 |
| 1 c.c. pit. (day 3–4) | 500 | 92.8 | 8.9 | 82.9 | 84 | 233 |
| | | Goat 2. | Lactating. | 42.5 kg. | | |
| Normal | 1993 | 93.4 | 16.1 | 77.3 | — | — |
| 1 c.c. pit. (day 1–2) | 850 | 93.2 | 6.0 | 87.2 | 442 | 1143 |
| 1 c.c. pit. (day 3–4) | 1430 | 93.4 | 8.9 | 84.5 | 340 | 563 |
| 1 c.c. pit. (day 5–6) | 1620 | 92.8 | 12.5 | 80.3 | 136 | 373 |
| | | Goat 3. | Non-lactating. | 32.7 kg. | | |
| Normal | 883 | 89.2 | 12.0 | 77.2 | — | — |
| 1 c.c. pit. (day 1–2) | 350 | 89.2 | 5.6 | 83.6 | 236 | 533 |
| 1 c.c. pit. (day 3–4) | 670 | 89.2 | 10.8 | 78.4 | 52 | 213 |
| 1 c.c. pit. (day 5–6) | 800 | 88.6 | 11.0 | 77.6 | — | 83 |
| | | Goat 4. | Non-lactating. | 39.4 kg. | | |
| Normal | 728 | 84.1 | 9.3 | 74.8 | — | — |
| 1 c.c. pit. (day 1–2) | 150 | 84.1 | 3.0 | 81.1 | 252 | 578 |
| 1 c.c. pit. (day 3–4) | 260 | 84.1 | 6.8 | 77.3 | 95 | 468 |

TABLE II.

| Period | c.c. urine | Total blood chlorine m.Eq. | Organic chlorine m.Eq. | Ionic chlorine m.Eq. | c.c. water retained (calculated) | c.c. water retained (found) |
|---|---|---|---|---|---|---|
| | | Goat 1. | Lactating. | 35 kg. | | |
| Normal | 2018 | 92.8 | 10.9 | 81.9 | — | — |
| 1 c.c. pit. (1st dose) | 1720 | 92.6 | 4.4 | 88.2 | 224 | 298 |
| 1 c.c. pit. (2nd dose) | 1500 | 92.8 | 2.8 | 90.0 | 280 | 518 |
| 1 c.c. pit. (3rd dose) | 1350 | 91.9 | 0.0 | 91.9 | 336 | 668 |
| | | Goat 2. | Lactating. | 42.5 kg. | | |
| Normal | 1179 | 93.4 | 16.4 | 77.0 | — | — |
| 1 c.c. pit. (1st dose) | 625 | 92.7 | 9.9 | 82.8 | 272 | 554 |
| 1 c.c. pit. (2nd dose) | 540 | 93.1 | 4.9 | 88.2 | 510 | 639 |
| 1 c.c. pit. (3rd dose) | 670 | 93.3 | 2.2 | 91.1 | 646 | 509 |
| | | Goat 3. | Non-lactating. | 32.7 kg. | | |
| Normal | 1488 | 88.4 | 12.5 | 75.9 | — | — |
| 1 c.c. pit. (1st dose) | 840 | 89.1 | 5.1 | 84.0 | 286 | 648 |
| 1 c.c. pit. (2nd dose) | 720 | 88.8 | 1.9 | 86.9 | 390 | 768 |
| 1 c.c. pit. (3rd dose) | 610 | 88.8 | 0.7 | 88.1 | 442 | 878 |
| | | Goat 4. | Non-lactating. | 39.4 kg. | | |
| Normal | 1832 | 84.1 | 9.9 | 74.2 | — | — |
| 1 c.c. pit. (1st dose) | 1230 | 84.1 | 2.7 | 81.4 | 320 | 602 |
| 1 c.c. pit. (2nd dose) | 1460 | 82.9 | 0.9 | 82.0 | 352 | 372 |
| 1 c.c. pit. (3rd dose) | 845 | 84.4 | 0.0 | 84.4 | 448 | 987 |

TABLE III.

*Percentage total and organic chlorine in the tissue of the goat.*

| | Tissue | Weight of tissue (kg.) | Total chlorine (mg. per cent) | Organic chlorine (per cent) | Ionizable chlorine (per cent) |
|---|---|---|---|---|---|
| Weight of 35 kg. goat | Kidney | 0.28 | 149.1 | 21.1 | 128.0 |
| | Heart | 0.14 | 108.0 | 26.0 | 82.0 |
| | Liver | 0.35 | 101.0 | 19.0 | 82.0 |
| | Lung | 0.18 | 220.6 | 40.6 | 180.0 |
| | Muscle | 16.28 | 50.4 | 10.4 | 40.0 |

TABLE IV.

*Retention of water by conversion of organic to ionic chlorine.*

| Tissue | Cubic centimetres of water retained to preserve osmotic equilibrium (approx.) |
|---|---|
| Kidney ... ... ... | 28 |
| Heart ... ... ... | 42 |
| Liver ... ... ... | 84 |
| Lung ... ... ... | 40 |
| Muscle ... ... ... | 4070 |

TABLE V.

*The effect of large doses of pituitrin on the water metabolism.*

| Period | c.c. urine | Total blood chlorine m.Eq. | Organic chlorine m.Eq. | Ionic chlorine m.Eq. |
|---|---|---|---|---|
| | | GOAT 1. | | |
| Normal | 733 | 92.8 | 10.9 | 81.9 |
| 3 c.c. pit. | | | | |
| (day 1–2) | 900 | 93.1 | 0.0 | 93.1 |
| (day 3–4) | 1000 | 92.4 | 1.9 | 90.5 |
| (day 5–6) | 1000 | 92.0 | 5.8 | 86.2 |
| | | GOAT 2. | | |
| Normal | 1993 | 93.4 | 16.1 | 77.3 |
| 3 c.c. pit. | | | | |
| (day 1–2) | 2800 | 93.4 | 0.0 | 93.4 |
| (day 3–4) | 3000 | 92.8 | 0.0 | 92.8 |
| (day 5–6) | 3150 | 92.6 | 8.2 | 84.2 |
| | | GOAT 3. | | |
| Normal | 883 | 89.2 | 12.0 | 77.2 |
| 3 c.c. pit. | | | | |
| (day 1–2) | 950 | 89.5 | 0.0 | 89.5 |
| (day 3–4) | 1035 | 87.4 | 0.0 | 87.4 |
| (day 5–6) | 965 | 88.3 | 4.3 | 84.0 |
| | | GOAT 4. | | |
| Normal | 728 | 84.1 | 9.3 | 74.8 |
| 3 c.c. pit. | | | | |
| (day 1–2) | 760 | 84.0 | 0.0 | 84.0 |
| (day 3–4) | 850 | 83.5 | 2.7 | 80.8 |
| (day 5–6) | 830 | 83.5 | 4.9 | 78.6 |